

WHAT IS CLAIMED IS:

1. A modulator of regulatory cellular events occurring intracellularly that are mediated by regulatory proteins containing a 'death domain' motif which is a regulatory portion of said proteins, said modulator being capable of interacting with one or more of the 'death domain' motifs contained in said regulatory proteins and affecting the regulatory action of one or more of said regulatory proteins.

2. A modulator according to claim 1, wherein said modulator is selected from the group comprising naturally-derived 'death domain' motif-binding proteins and peptides and analogs and derivatives thereof capable of interacting with one or more of said 'death domain' motifs.

3. A modulator according to claim 1, wherein said modulator is selected from the group of synthetically produced complementary peptides, synthesized by using as substrates the 'death domain' motif sequences of said regulatory proteins containing 'death domain' motifs, said complementary peptides being capable of interacting with one or more of said 'death domain' motifs.

4. A modulator according to claim 1, wherein said modulator is selected from the group consisting of organic compounds capable of interacting with one or more of said 'death domain' motifs, said organic compounds being derived

from known compounds and selected by using said 'death domain' motifs as a substrate in a binding assay, or being synthesized using said 'death domain' motifs as a substrate for designing and synthesizing said organic compounds.

5. A modulator according to claim 1, wherein said modulator is selected from the group consisting of peptides or polypeptides derived from naturally-occurring 'death domain' motif sequences, said peptides or polypeptides being capable of interacting with one or more of said 'death domain' motifs, and analogs and derivatives of said peptides or polypeptides capable of interacting with one or more of said 'death domain' motifs.

6. A modulator according to claim 1, wherein said modulator is further characterized by being capable of recognizing the general 'death domain' motif sequence features common to the 'death domain' motifs of 'death domain' motif containing proteins, and being capable of recognizing one or more of the specific 'death domain' motifs of said proteins, said specific sequence features being specific to each 'death domain' motif sequence of each of said proteins.

7. A modulator according to claim 1, wherein said modulator is capable of interacting with one or more of the 'death domain' motifs contained within the proteins belonging

201909041003409

to the group comprising p55 TNF-R, FAS-R, NGF-R, MORT-1, RIP, TRADD and ankyrin 1.

8. A modulator according to claim 7, wherein said modulator is further characterized by being capable of interacting with sequence features which the 'death domain' motifs of said group of proteins have in common, said common sequence features comprising the group of common amino acid residues W (tryptophan), L (leucine), I (isoleucine), A (alanine), D (aspartic acid), E (glutamic acid), T (threonine), R (arginine) and Y (tyrosine) at the location within said 'death domain' motifs of SEQ ID NOS:1-5.

9. A DNA sequence encoding a modulator being a protein, peptide or polypeptide or an analog of any thereof, according to claim 1.

10. A DNA sequence according to claim 9, encoding a naturally-derived protein or peptide, selected from the group consisting of:

(a) a cDNA sequence derived from the coding region of a native 'death domain' motif-binding protein or peptide;

(b) DNA sequences capable of hybridization to a sequence of (a) under moderately stringent conditions and which encode a biologically active 'death domain' motif-binding protein or peptide; and

(c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (a) and (b) and which encode a biologically active 'death domain' motif-binding protein or peptide.

11. A sequence according to claim 9, encoding a 'death domain' motif-binding protein or peptide capable of binding to the 'death domain' motif of one or more of the proteins selected from the group consisting of p55 TNF-R, FAS-R, NGF-R, MORT-1, RIP, TRADD and ankyrin 1.

12. A DNA sequence according to claim 9, encoding a peptide or polypeptide derived from the naturally-occurring 'death domain' motif sequence of the 'death domain' motif-containing proteins.

13. A DNA sequence according to claim 12, encoding a peptide or polypeptide derived from the 'death domain' motif sequence of any one of the proteins of the group comprising p55 TNF-R, FAS-R NGF-R, MORT-1, RIP, TRADD and ankyrin 1.

14. A protein, peptide or polypeptide, or an analog of any one thereof, encoded by a DNA sequence according to claim 9, said protein, peptide, polypeptide or analog being capable of binding to or interacting with one or more of the 'death domain' motifs of one or more 'death domain' motif-containing proteins.

15. A vector comprising a DNA sequence according to claim 9.

16. A vector according to claim 15, which is capable of being expressed in a eukaryotic host cell.

17. A vector according to claim 15, which is capable of being expressed in a prokaryotic host cell.

18. Transformed eukaryotic or prokaryotic host cells containing a vector according to claim 15.

19. A method for producing a protein, peptide, polypeptide or analog which is capable of binding to or interacting with one or more of the 'death domain' motifs of one or more 'death domain' motif-containing proteins, comprising growing the transformed host cells according to claim 18 under conditions suitable for the expression of said protein, peptide, polypeptide or analog, effecting post-translational modifications of said protein, peptide, polypeptide or analog as necessary for obtention thereof, and extracting said expressed protein, peptide, polypeptide or analog from culture medium of said transformed cells or from cell extracts of said transformed cells.

20. A method for the modulation of the TNF or FAS-R ligand effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankyrin 1 or by other proteins containing a 'death domain'

motif, comprising treating said cells with one or more proteins, peptides, polypeptides or analogs selected from the group consisting of the proteins, peptides, polypeptides or analogs according to claim 14, all being capable of binding to or interacting with the 'death domain' motif and modulating the activity of said 'death domain' motif-containing proteins, wherein said treating of said cells comprises introducing into said cells said one or more proteins, peptides, polypeptides or analogs in a form suitable for intracellular introduction thereof, or introducing into said cells a DNA sequence encoding said one or more proteins, peptides, polypeptides or analogs in the form of a suitable vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells.

21. A method for the modulation of the TNF or FAS-R ligand effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankyrin 1 or by other proteins containing a 'death domain' motif, comprising:

(a) constructing a recombinant animal virus vector carrying a sequence encoding a viral surface protein (ligand) that is capable of binding to a specific cell surface receptor on the surface of said cell to be treated and a second

sequence encoding a protein selected from the proteins, peptides, polypeptides and analogs according to claim 14, said protein, peptide, polypeptide or analogs, when expressed in said cells being capable of modulating the activity of said 'death domain' motif-containing protein, and

(b) infecting said cells with said vector of (a).

22. A method for modulating the TNF or FAS-R ligand effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankryrin 1 or by other proteins containing a 'death domain' motif, comprising treating said cells with antibodies, or active fragments or derivatives thereof, specific for a protein, peptide, polypeptide, or analog in accordance with claim 14, said treating being by application of a suitable composition containing said antibodies, active fragments or derivatives thereof to said cells, said composition being formulated for intracellular application.

23. A method for modulating the TNF or FAS-R ligand effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankryrin 1 or by other proteins containing a 'death domain' motif, comprising treating said cells with an oligonucleotide sequence encoding an antisense sequence of at least part of the sequence according to claim 9, said oligonucleotide

sequence being capable of blocking the expression of at least one of the 'death domain' motif-binding proteins or peptides.

24. A method according to claim 23, wherein said treating of said cells is by transfection of said cells with a recombinant animal virus vector comprising the steps of:

(a) constructing a recombinant animal virus vector carrying a sequence encoding a viral surface protein (ligand) that is capable of binding to a specific cell surface receptor on the surface of said cell to be treated and in a second sequence encoding said oligonucleotide sequence; and

(b) infecting said cells with said vector of (a).

25. A method for treating tumor cells or HIV-infected cells or other diseased cells, comprising:

(a) constructing a recombinant animal virus vector carrying a sequence encoding a viral surface protein that is capable of binding to a specific tumor cell surface receptor or HIV-infected cell surface receptor or receptor carried by other diseased cells and a sequence encoding a protein selected from the group consisting of the proteins, peptides, polypeptides and analogs of claim 14, said protein, peptide, polypeptide or analog when expressed in said tumor, HIV-infected, or other diseased cell, being capable of killing said cell; and



(b) infecting said tumor or HIV-infected cells or other diseased cells with said vector of (a).

26. A method for modulating the TNF or FAS-R ligand effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankyrin 1 or by other proteins containing a 'death domain' motif, comprising applying the ribozyme procedure in which a vector encoding a ribozyme sequence capable of interacting with a cellular mRNA sequence encoding a protein or peptide according to claim 14, is introduced into said cells in a form that permits expression of said ribozyme sequence in said cells, and wherein when said ribozyme sequence is expressed in said cells it interacts with said cellular mRNA sequence and cleaves said mRNA sequence resulting in the inhibition of expression of said protein or peptide in said cells.

27. A method for isolating and identifying proteins, peptides, factors or receptors capable of binding to the 'death domain' motif-binding proteins or peptides according to claim 14, comprising:

(a) applying the procedure of affinity chromatography in which said protein or peptide is attached to the affinity chromatography matrix;

(b) bringing said attached protein into contact with a cell extract; and

(c) eluting, isolating and analyzing any proteins, factors or receptors from the cell extract which bound to said attached protein.

28. A method for isolating and identifying proteins capable of binding to the 'death domain' motif-binding proteins or peptides according to claim 14, comprising applying the yeast two-hybrid procedure in which a sequence encoding said 'death domain' motif-binding protein is carried by one hybrid vector and a sequence from a cDNA or genomic DNA library is carried by the second hybrid vector, the vectors then being used to transform yeast host cells and the positive transformed cells are isolated, followed by extraction of said second hybrid vector to obtain a sequence encoding a protein which binds to said 'death domain' motif-binding protein.

29. A pharmaceutical composition for the modulation of the TNF or FAS-R ligand-effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankyrin 1, or by other proteins containing a 'death domain' motif, comprising, as active ingredient, a modulator according to claim 1.

30. A pharmaceutical composition for modulating the TNF or FAS-R ligand effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankyrin 1, or by other proteins containing a

'death domain' motif, comprising, as active ingredient, a recombinant animal virus vector encoding a protein capable of binding a cell surface receptor and encoding a protein or peptide or analogs thereof according to claim 14.

31. A pharmaceutical composition for modulating the TNF or FAS-R ligand effect on cells mediated by p55 TNF-R and FAS-R, or the functions mediated in cells by NGF-R, MORT-1, RIP, TRADD, ankyrin 1, or by other proteins containing a 'death domain' motif, comprising, as active ingredient, an oligonucleotide sequence encoding an antisense sequence of the sequence according to claim 9.

32. A method for isolating and identifying a protein capable of binding to the 'death domain' motifs of 'death domain' motif-containing proteins, comprising applying the procedure of non-stringent Southern hybridization followed by PCT cloning, in which a sequence, or parts thereof, according to claim 9 is used as a probe to bind sequences from a cDNA or genomic DNA library, having a least partial homology thereto, said bound sequences then being amplified and cloned by the PCR procedure to yield clones encoding proteins having at least partial homology to said sequences of claim 9.

33. A method for modulating the concerted intracellular modulation resulting from the indirect interaction between the FAS-R and the p55 TNF-R, via their

cascading interaction of MORT-1 and TRADD, or MORT-1 and RIP, comprising, treating cells with a modulator which will enhance or inhibit the MORT-1-TRADD or MORT-1-RIP mediated p55 TNF-R-FAS-R interaction.